REMARKS

Claims 1-7, 10, and 14-30 are pending.

THE AMENDMENTS

The amendments to the specification (and replacement "marked-up" version of prior amendments) are intended to correct, or accurately reflect earlier corrections of, errors that are clear in context to one of ordinary skill in the art. These corrections are not intended to narrow or otherwise change the scope of any of the terms of any of the claims.

The amendments to the claims are intended to focus on a different set of preferred treating agents. These amendments are not intended to narrow or otherwise change the scope of any of the terms of any of the claims, for any patentability or other reason. Applicants expressly reserve the right to pursue the original versions of these amended claims in any additional related application that may be pending or filed, or to re-introduce these claims in the instant application, if warranted.

Marked-up copies of the amendments are attached as Appendix A; a complete set of pending claims is attached as Appendix B.

THE SCOPE OF THE CLAIMED WATER-INSOLUBLE POLYMERS

During the Interview conducted today, the undersigned and the Examiner discussed the scope of the claimed water-insoluble polymers, described in all pending claims as "a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer." The undersigned agreed to submit further discussion supporting the scope of this description.

These particular properties of the water insoluble polymer, in combination with a water soluble polymer, are what gives the claimed formulation the ability to provide the

particular advantages reflected in the claims: controlled, extended release and progressive hydration of a treating agent.[1]

No art of record -- in any combination -- teaches, suggests, or discloses specifically the use of both a water soluble polymer and any water insoluble polymer at the same time -- let alone specifically a water insoluble, water swellable, cross-linked polycarboxylic polymer, and let alone in a manner that enables the treating agent to be hydrated only progressively.[2] No art of record -- in any combination -- teaches, suggests, or discloses for any formulation the particular advantages achieved by the instant formulations -- extended, controlled release and progressive hydration of a treating agent.

Accordingly, there is no proper suggestion or motivation to be found in any art of record, alone or in any combination, regarding the use of both a water soluble polymer and a water insoluble, water swellable, cross-linked polycarboxylic polymer in a formulation prepared in a manner to provide both extended, controlled release and progressive hydration of a treating agent.

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[1] Similar use and advantages of the same group of polymers have been discussed or claimed broadly in other U.S. patents, for example, such as the following patents owned by the same assignee: U.S. Patents Nos. 4,615,697, 4,983,392, and 5,225,196 (each entitled "Bioadhesive Compositions And Methods Of Treatment Therewith"); 5,543,150 ("Method Of Progesterone Delivery And Affect Thereof"); 5,667,492 ("Use And Composition Of An Anti-Sexually Transmitted Diseases Formulation"); 5,985,861 and 6,054,447 (each entitled "Progesterone For Treating Or Reducing Ischemia"); and 6,126,959 ("Pharmaceutical Composition For Treating Dysmenorrhea And Premature Labor").

[2] As discussed, for example, in the Amendment and Response filed March 6, 2002, at page 12, in the Amendment and Response filed October 25, 2001, at pages 10-12, and in the Amendment and Response filed April 24, 2001, at pages 7-9, the mere inclusion of similar ingredients does not mean that the ingredients were combined in a manner that could provide progressive hydration, because most standard tabletting methods are "wet" methods.

THE REJECTIONS

Rejection of Claims Under 35 U.S.C. § 102(a, e)

The Office Action maintains the rejection of claims 1, 3-5, 7, 14-16, 21-25, 29, and 30 under 35 U.S.C. § 102(a, e). The Advisory Action notes that

> "progressive hydration" is an inherent property of Timpe's composition/method since Timpe's composition has the same limitations as the instant invention. Examiner suggests that applicant include unobvious % ranges, not covered by the prior art, in instant invention responsible for the "progressive hydration."

Applicants respectfully disagree with this conclusion.[3] Timpe's focus and disclosure are inconsistent with the instant invention, and thus should not be understood to raise any patentability issue. (1) Timpe does not teach or disclose use of the two key polymer types used in the instant invention -- one water soluble polymer, and one particular water insoluble polymer, that is, a bioadhesive, water-swellable cross-linked polycarboxylic polymer. Timpe's examples only use water soluble polymers. However, the instant invention uses the two polymer types specifically at the same time to counter-balance each other, relying crucially on their opposite water-solubility properties. There is absolutely no teaching or recognition in the art of record that this particular combination -- or indeed any combination of water soluble and water insoluble polymers -- could be used to provide the benefits that result from the claimed invention. (2) Timpe teaches a quick release structure and formulation intended to increase the speed of the treating agent's release and

[3] Applicants previously argued that Timpe is distinguished from the instant invention because Timpe does not teach or disclose use of a dry preparation, or, therefore, progressive hydration. Applicants have since realized that this argument may not apply to distinguish the instant invention from Timpe. Wet methods, if they include an appropriate and effective drying phase and depending on when the active ingredient is introduced to the formulation, apparently may still be used to prepare a progressive hydration formulation. While there is no indication that Timpe contemplates or uses such a drying phase, Applicants hereby expressly retract any reliance or pursuit of that particular argument or distinction. However, Applicants reserve the right to further examine this issue in the future, and to re-state the argument, should it become warranted or appropriate to do so.

availability, focusing on a formulation which includes (as reflected in Timpe's examples) only a water-soluble polymer. This formulation is completely consistent with Timpe's goal, but cannot provide extended, controlled release, or progressive hydration, of a treating agent.

(1) Timpe Does Not Teach Combining The Two Polymer Types.

Timpe does not teach or disclose use of a combination of a water soluble polymer and a water insoluble polymer at all, let alone the type of water insoluble polymer claimed here. In contrast, the instant invention uses only a combination of the two types of polymers, specifically for their distinct, opposing properties. And the claimed water insoluble polymer specifically is a bioadhesive, water swellable cross-linked polycarboxylic polymer -- which is not used by Timpe's examples at all. This particular water insoluble polymer appears only as one of a laundry list of "bioadhesive adjuvants" listed in Timpe's disclosure, without any recognition or suggestion of special significance or of any distinction from any of the water soluble polymers.

As recognized in the instant application, the greater the proportion of the water-soluble polymer in the claimed formulation, the less time it takes for the formulation to progressively hydrate. See, the instant specification at page 27, lines 1-12 (as amended above). The water-soluble polymer also is used to provide the initial bioadhesion. See, e.g., the instant specification, at page 3, lines 23-29.

Of course, as one of ordinary skill in the art would expect, and as common sense suggests, a water soluble polymer -- if not already hydrated -- by definition tends to hydrate quickly. Instant specification, at page 2, line 30 to page 3, line 4. In contrast, the water-

insoluble, water-swellable polymer provides the extended bioadhesion, see page 3, lines 5-9, and the extended hydration, and extended release, of the treating agent.

None of Timpe's examples uses any water-insoluble polymer at all, alone or in combination with a water-soluble polymer. Accordingly, Timpe does not disclose or suggest -- and in fact, cannot disclose or suggest -- the advantages to using such a water insoluble polymer in combination with a water soluble polymer, especially in a formulation designed to provide progressive hydration and controlled, extended release.

(2) Timpe Teaches A Quick Release Structure, Not Extended Release.

The problem addressed by Timpe was "improv[ing] the passage of the active agents contained [in the bioadhesive tablets] through the mucosa." Col. 2, lines 46-49. Timpe solves the problem "according to [Timpe's] invention by a bioadhesive tablet containing at least one bioadhesive adjuvant and at least one lubricant, with at least one surface of said tablet comprising concentric or parallel, straight and/or curved depressions." Col. 2, lines 52-56. Thus, Timpe teaches that only one bioadhesive is needed; his examples all contain only one bioadhesive polymer.

Timpe discloses a ridged formulation, increasing the surface area of the tablet, from which "active ingredients are made available for resorption across an extensive tissue area of the target organ." Col. 2, lines 60-65. Timpe's bioadhesive tablets "nearly completely release the active agent they contain and stimulate its resorption by the tissue." Col. 2, line 66 to col. 3, line 2. Timpe's invention incorporates ridges so that the products "do not impair by swelling the passage of the active agents they contain through the mucosa." Col. 2, lines 52 to 60. "**The medicinal substance ... can easily pass through [through the**

tablet] in those part of the depressions that are not in contact with the mucosa, thus guaranteeing high bioavailability." Col. 5, lines 41-45.

Thus, Timpe's entire focus is on delivering more treating agent, more quickly. This is essentially the opposite of the goal of a formulation intended to hydrate progressively, and to provide controlled release of the treating agent over an extended period of time. There is no teaching or suggestion at all in Timpe that any formulation, let alone the contemplated combination of polymers, could provide progressive hydration and controlled, extended release of a treating agent. Again, this is not unexpected, because the instant invention simply addresses a problem contrary to Timpe's goal of quick release and availability of the treating agent.

Rejection of Claims Under 35 U.S.C. § 103(a)

The Office Action maintains the rejection of all claims under 35 U.S.C.§ 103(a). The Office Action refers to the response regarding the rejection under Section 102.

Applicants respectfully disagree with this conclusion. As discussed further above, Timpe does not disclose use of any formulation that uses both a water insoluble polymer and a water soluble polymer. There is no teaching or disclosure involving the particular water-insoluble polymer involved in the instant invention, or the unique benefits that result. There is no teaching or suggestion that Timpe's contemplated formulations could provide progressive hydration or extended, controlled release of the treating agent over a prolonged period of time. Indeed, Timpe's whole focus is inconsistent with the instant invention -- Timpe wanted to produce quick, complete release and availability of the treating agent.

Conclusion

In light of these remarks, Applicants respectfully request reconsideration and withdrawal of the rejections. It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. **Should the Examiner disagree with this position, Applicants request a further personal or telephonic interview as soon as possible, to discuss any remaining issues or clarifications in an effort to expeditiously advance the application toward allowance.**

The fees for a Request for Continued Examination and for two months' extension of time are believed to be $1,140.00 due for this submission. Please charge the required fees to Winston & Strawn Deposit Account No. 501-814.

Respectfully submitted,

Dated: November 4, 2002

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APPENDIX A

The corrected marked-up version of the paragraph in the Specification at page 15, line 32 to page 16, line 10 of the Specification reads as follows:

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the materials of construction can be varied to optimize the desired characteristics of the tablet. For example, the present inventors have discovered that [, quite unexpectedly,] by progressively increasing [decreasing] the amount of lactose and corn starch and progressively decreasing [increasing] the amount of carbomer 974P [934P], the amount of time it takes a tablet to hydrate is progressively increased. Accordingly, as will be appreciated by one of ordinary skill in the art, tablets suited for specific treatments (i.e., specific active, specific dose, specific delivery time) can be manufactured.

The marked-up, amended paragraph at page 27, lines 1-12, reads as follows:

As shown in the charts and tables, by decreasing the amount of lactose and corn starch and increasing the amount of carbomer 974P [934P], the time it takes for the tablet to hydrate is progressively decreased [increased]. Formulation 1 (0069904) and others like it with high levels of carbomer 974P [934P] and low levels of lactose and corn starch are probably best suited to buccal administration where 12 hours of delivery is usually sufficient [for vaginal administration where release is often required over a period of days]. In the first example given above Formulation 8 (0029906), where the levels of lactose and corn starch are high and carbomer 974P [934P] is low, the formula is probably better suited for vaginal administration where release is often required over a period of days [to buccal administration where 12 hours of delivery is usually sufficient].

The marked-up version of amended claims 1 and 7 read as follows:

1. (Three times amended) A controlled, sustained release progressive hydration pharmaceutical composition in the form of a tablet, comprising:

an effective amount of an active ingredient that is [metabolized by 5α-reductase] a sex hormone,

a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer, and

a water soluble polymer,

wherein said composition is formulated in a dry state to deliver, upon administration of said tablet to a mucosal surface of a mammal, said active ingredient to the bloodstream of said mammal.

7. (Twice amended) A method of delivering to a mammal a sex hormone [an active ingredient that is metabolized by 5α-reductase], comprising administering said [active ingredient] sex hormone via a progressive hydration bioadhesive composition to a mucosal surface of the mammal, wherein said composition is formulated as a dry tablet that includes

(a) said [active ingredient] sex hormone,
(b) a bioadhesive, water insoluble, water swellable cross-linked polycarboxylic polymer, and
(c) a water-soluble polymer.

APPENDIX B

Biodhesive Progressive Hydration Tablets
Pending Claims: 1-7, 10, 14-30

1. (Three times amended) A controlled, sustained release progressive hydration pharmaceutical composition in the form of a tablet, comprising:

an effective amount of an active ingredient that is a sex hormone,
a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer, and
a water soluble polymer,

wherein said composition is formulated in a dry state to deliver, upon administration of said tablet to a mucosal surface of a mammal, said active ingredient to the bloodstream of said mammal.

2. The composition of claim 1, wherein said active ingredient is present in about 50% by weight or less.

3. The composition of claim 1, wherein active ingredient is testosterone or progesterone.

4. The composition of claim 3, wherein said composition is formulated to deliver said active ingredient via the mammal's vaginal cavity.

5. The composition of claim 3, wherein said composition is formulated to deliver said active ingredient via the mammal's buccal cavity.

6. (Twice amended) A progressive hydration pharmaceutical composition comprising:

an effective amount of testosterone at about 1% to about 30% by weight,
a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer,
and a water soluble polymer,

wherein said composition is formulated to progressively hydrate and to deliver said testosterone to the bloodstream of a mammal through a mucosal surface of the mammal.

7. (Twice amended) A method of delivering to a mammal a sex hormone, comprising administering said sex hormone via a progressive hydration bioadhesive composition to a mucosal surface of the mammal, wherein said composition is formulated as a dry tablet that includes

(a) said sex hormone,
(b) a bioadhesive, water insoluble, water swellable cross-linked polycarboxylic polymer, and
(c) a water-soluble polymer.

10. (Amended) A method of delivering testosterone to a mammal, comprising administering said testosterone via a progressive hydration composition through a mucosal surface of the mammal, wherein the composition comprises:

a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer,
a water soluble polymer, and
said testosterone,

and wherein said method provides a blood serum concentration ration of testosterone to 5α-dydrotestosterone (DHT) of about 10 to 1 or greater in the bloodstream of said mammal.

14. (Amended) A controlled, sustained release progressive hydration composition for delivering testosterone to the bloodstream of a mammal, comprising:

a bioadhesive, water insoluble cross-linked polycarboxylic polymer,
a water soluble polymer,
and about 1% to about 30% by weight testosterone,

wherein said composition is formulated to deliver said testosterone through a mucosal surface of the mammal, and to provide a blood serum concentration ratio of testosterone to 5α-dihydrotestosterone (DHT) of about 10 to 1 or greater in the bloodstream of said mammal.

15. (Amended) The composition of claim 1, wherein said composition is formulated to deliver said active ingredient via the mammal's nasal cavity.

16. (Amended) The composition of claim 1, wherein said composition is formulated to deliver said active ingredient via said mammal's rectal cavity.

17. The pharmaceutical composition of claim 6, wherein said composition is formulated to deliver said testosterone via the mammal's buccal cavity.

18. The pharmaceutical composition of claim 6, wherein said composition is formulated to deliver said testosterone via the mammal's vaginal cavity.

19. The method of claim 10, wherein said composition is administered through the mammal's buccal cavity.

20. The method of claim 10, wherein said composition is formulated is administered through the mammal's vaginal cavity.

21. The controlled, sustained release progressive hydration composition of claim 14, wherein said composition is formulated to deliver said testosterone via the mammal's buccal cavity.

22. The controlled, sustained release progressive hydration composition of claim 14, wherein said composition is formulated to deliver said testosterone via the mammal's vaginal cavity.

23. (Amended) A progressive hydration pharmaceutical composition comprising:

testosterone,
a bioadhesive, water insoluble, water-swellable cross-linked polycarboxylic polymer,
and a water soluble polymer,

wherein said composition is formulated to progressively hydrate and to deliver a therapeutically effective amount of said testosterone to the bloodstream of a mammal through a mucosal surface of the mammal.

24. The pharmaceutical composition of claim 23, wherein said composition is formulated to deliver said testosterone via the mammal's buccal cavity.

25. The pharmaceutical composition of claim 23, wherein said composition is formulated to deliver said testosterone via the mammal's vaginal cavity.

26. A controlled, sustained release progressive hydration composition for delivering testosterone to the bloodstream of a mammal, comprising:

a bioadhesive, water insoluble cross-linked polycarboxylic polymer,
a water soluble polymer,
and testosterone,

wherein said composition is formulated to deliver said testosterone through a mucosal surface of the mammal, and to provide a blood serum concentration ratio of testosterone to 5α-dihydrotestosterone (DHT) of about 10 to 1 or greater in the bloodstream of said mammal.

27. The controlled, sustained release progressive hydration composition of claim 26, wherein said composition is formulated to deliver said testosterone via the mammal's buccal cavity.

28. The controlled, sustained release progressive hydration composition of claim 26, wherein said composition is formulated to deliver said testosterone via the mammal's vaginal cavity.

29. The method of claim 7, wherein said mucosal surface is the mammal's vaginal cavity.

30. The method of claim 7, wherein said mucosal surface is the mammal's buccal cavity.